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DATE: September 21, 2004

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FROM: Kelly J. Williamson
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In re:	Stein *et al.*	Confirmation No.:	5877
Appl. No.:	09/973,375	Group No.:	1617
Filed:	October 9, 2001	Examiner:	S. Jiang
For:	METHODS FOR THE TREATMENT OF A TRAUMATIC CENTRAL NERVOUS SYSTEM INJURY		

Attachments:
Request for two month extension (1 page)
Amendment After Final (9 pages)
Interview Summary (5 pages)

NO. OF PAGES: 16 (Including cover page)	**OPERATOR:**

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Attorney's Docket No. 007157/239838 PATENT

RESPONSE UNDER 37 C.F.R. 1.116 - EXPEDITED PROCEDURE - EXAMINING GROUP 1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Stein *et al.*	Confirmation No.:	5877
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INTERVIEW SUMMARY

Sir:

An interview in the above-referenced matter occurred on September 14, 2004 between Examiner Jiang, Examiner Padmanabhan, and Examiner Caputa, Applicants representatives Murray Spruill and Kelly Williamson, and the inventors Donald Stein and Stuart Hoffman. Applicants provide below a summary of the interview.

The rejection under 35 U.S.C. §103 set forth in the Final Office Action mailed April 21, 2004 was discussed. Applicants discussed both the Amendment and Response filed on December 19, 2003 and the Declaration filed under 37 C.F.R. 1.132 also filed on December 19, 2003. Applicants emphasized the following points during the interview.

1. Applicants pointed out that sufficient argument and evidence to overcome the rejection under 35 U.S.C. §103 has been made of record. A declaration filed under CFR 1.132 on December 19, 2003 by a third party expert is of record stating that one of skill in the art would not presume that compounds with similar structures, such as progesterone and allopregnanlone, would have the same activity. The teachings of Nilsen *et al.* (2003) *Endocrinology 143*:205-212, Pham *et al.* (2003) *21st Annul National Neurotrauma*

Society Symposium Abstract P133, and Ghoumri *et al.* (2003) *J. Neurochem 86*:848-59, which were made of record in the 132 declaration, were discussed in detail to support this point. The cited art therefore failed to provided sufficient motivation or a reasonable expectation of success for one of skill to arrive at the claimed invention.

2. The declaration filed under 37 C.F.R. 1.132 on December 19, 2003 addressed inaccurate scientific conclusions being drawn to assemble the 103 rejection. Applicants maintained that the declaration must be considered by the Examiner or a further explanation of the defects in the declaration be provided.

3. The Examiner indicated that the discussion in the 132 declaration regarding the possible mechanism of action of allopregnanolone and progesterone was irrelevant since the mechanism of action of treatment does not have a bearing on the patentability of the invention. Applicants emphasized that the discussion of the mechanism of action of allopregnanolone and progesterone appears in the 132 declaration because, in formulating the 103 rejection, *the Examiner repeatedly asserts that progesterone and its metabolites, such as allopregnanolone, are known to share the same mechanism of action*. The 132 declaration is therefore addressing the specific rejections set forth by the Examiner and therefore the declaration should be considered.

4. Applicants discussed the scientific inaccuracy of the assertion appearing on page 5, lines 14-16 of the Office Action mailed April 21, 2004 which states "allopregnanolone is also known to possess higher potency and efficacy than progesterone" based on the teachings of Gee *et al.* Applicants emphasized section 4a of the 132 declaration which stated that Gee *et al.* teach that both progesterone and many of its metabolites bind with high affinity to a unique GABA/GBR complex and that these metabolites delay onset of myoclonus following TBPS induced seizures in mice. *There is no data demonstrating that progesterone and allopregnanolone are effective at treating other disease states,*

such as traumatic brain injury, and certainly no teaching that *all* of progesterone's beneficial effects are related to progesterone's conversion into its various metabolites.

5. Applicants discussed the scientific inaccuracy of the assertion appearing on page 5, lines 14-16 of the April 21, 2004 Office Action that stated "progesterone and its metabolites such as allopregnanolone are known to share the same mechanism of action on their neuroprotective effects through their interaction with GABA." Sections 4b, 4c, 4d, and 4e of the 132 declaration, which outline that the mechanism of action by which progesterone and allopregnanolone mediate their neuroprotective effects is *unknown*, were discussed. It was further discussed that one of skill would not assume that progesterone and allopregnanolone have identical mechanisms of action. The assumption that compounds with similar precursors or structures have identical mechanisms of action is flawed. In support of this conclusion, Applicants discussed in detail the various references cited in section 4c of the 132 declaration.

6. Applicants discussed the scientific inaccuracy of the assertion appearing on page 4, first paragraph and page 5, lines 15-20 of the Office Action mailed April 21, 2004 which asserts that Roof *et al.* (1997) teaches that "progesterone's neuroprotective effects are through its interaction with GABA, and progesterone and some of its metabolites are known to bind to and potentiate activity of GABAa receptor." Sections 4b and 4c of the declaration which demonstrate that the neuroprotective effects of progesterone remain unknown and could act via several biological mechanisms were discussed. It was again emphasized that Roof *et al.* (1997) speculate that progesterone could act via "radical scavenging and membrane stabilization" (page 7, paragraph 2), could interact with GABAa receptor, and/or antagonize the glutamate receptor system (page 7, paragraph 3). Roof *et al.* all never concludes progesterone's neuroprotective activity results from *only* GABA receptor modulation.

7. Applicants emphasized that a traumatic central nervous system injury does not simply disrupt the GABA receptor system. A traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss.* Modulation of only the GABA receptor provides no assurances that one could treat a traumatic central nervous system injury as asserted in the Office Action.

8. Applicants discussed the scientific inaccuracy of the assertion appearing on page 5, last paragraph and page 6, lines 1 and 2 of the April 21, 2004 Office Action which states that allopregnanolone and progesterone have the "the same therapeutic usefulness." Applicants emphasized that neither the cited art nor the 132 declaration support this conclusion. Applicants discussed evidence appearing in the 132 declaration that outlined that the mechanism of action by which progesterone and allopregnanolone mediate their neuroprotective effects is unknown and further that one of skill would not assume progesterone and allopregnanolone have identical mechanisms of action.

9. The assertion appearing on page 9 of the Office Action dated April 21, 2004 was discussed. Specifically, the Office Action states "Applicant clearly acknowledges that progesterone and its particular metabolite, allopregnanolone, have the same therapeutic usefulness" in view of Examples 6 and 7 of the present application. Applicants emphasized that they never stated or suggested that progesterone and allopregnanolone have the same therapeutic usefulness. Examples 6 and 7, which administer progesterone to subjects, do not represent examples of the invention presently being claimed. Applicants requested the assertion regarding Applicant's admission be withdraw. If the assertion is maintained, Applicants requested authority for this conclusion.

No agreement was reached regarding the rejection under 35 U.S.C. §103. Examiner Caputa indicated Applicants would be contacted within two weeks by the Examiner to discuss the status of the case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Pamela Lockley 9/21/04

Pamela Lockley Date